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Effects of Long-Term Selenium Supplementation on the Incidence of Type 2 Diabetes

A Randomized Trial

Saverio Stranges, MD, PhD; James R. Marshall, PhD; Raj Natarajan, MS; Richard P. Donahue, PhD; Maurizio Trevisan, MD; Gerald F. Combs, PhD; Francesco P. Cappuccio, MD; Antonio Ceriello, MD; and Mary E. Reid, PhD

Background: Findings from animal models suggest that selenium supplementation improves glucose metabolism.

Objective: To examine the effect of long-term selenium supplementation on the incidence of type 2 diabetes.

Design: Secondary analysis of a randomized, double-blind, placebo-controlled trial.

Setting: Areas of low selenium consumption of the eastern United States.

Patients: 1202 persons seen in dermatology clinics who did not have type 2 diabetes at baseline.

Intervention: Oral administration of selenium, 200 μg/d, or placebo.

Measurements: Incidence of type 2 diabetes.

Results: During an average follow-up of 7.7 years (SD, 2.7), type 2 diabetes developed in 58 selenium recipients and 39 placebo recipients (incidence, 12.6 cases per 1000 person-years vs. 8.4 cases per 1000 person-years, respectively; hazard ratio, 1.55 [95% CI, 1.03 to 2.33]). The lack of benefit of selenium supplementation on the incidence of type 2 diabetes persisted in analyses stratified by age, sex, body mass index, and smoking status. An exposure–response gradient was found across tertiles of baseline plasma selenium level, with a statistically significantly increased risk for type 2 diabetes in the highest tertile of baseline plasma selenium level (hazard ratio, 2.70 [CI, 1.30 to 5.61]).

Limitations: Diabetes was a secondary outcome in the parent trial. Diagnoses of diabetes were self-reported but were validated in most participants. The sample was mostly older and white.

Conclusions: Selenium supplementation does not seem to prevent type 2 diabetes, and it may increase risk for the disease.

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For author affiliations, see end of text.

Insulin resistance, impaired glucose tolerance, and type 2 diabetes are all linked to oxidative stress, which may be the pathogenic mechanism that links these conditions to cardiovascular disease (1). Observational epidemiologic studies show a protective association of dietary or plasma antioxidants against the development of type 2 diabetes (2, 3). However, the few clinical trials that have examined the efficacy of antioxidant supplementation in the prevention of type 2 diabetes or its complications have had negative results (4–6). Experimental evidence from animal models suggests that supplementation with low doses of the antioxidant selenium may exert beneficial effects on glucose metabolism, possibly through many insulin-like actions, and may delay complications of diabetes. The effects of high-dose selenium supplements, however, are less clear (7–10). Some studies in patients with diabetes suggest that selenium supplementation may help to prevent vascular complications (11) and that diabetic patients may be deficient in selenium relative to healthy persons (12). Conversely, recent findings from the SU.VI.MAX (Supplementation with Antioxidant Vitamins and Minerals) study (13) showed no effect of supplementation with a combination of antioxidants, including selenium (100 μg/d), on fasting plasma glucose levels after 7.5 years of follow-up.

Because no randomized, placebo-controlled clinical trials to date have tested the effect of long-term supplementation with selenium alone (200 μg/d) on the risk for type 2 diabetes, we examined the efficacy of selenium supplementation in preventing new-onset type 2 diabetes in the NPC (Nutritional Prevention of Cancer) trial, a randomized, double-blind clinical trial designed primarily to evaluate the efficacy of selenium supplementation for prevention of cancer (14, 15). Specifically, we assessed the incidence of type 2 diabetes as a secondary end point throughout the blinded phase of the trial (1983–1996) among participants who did not have type 2 diabetes at baseline ($n = 1202$).

METHODS

Design and Participants

The rationale, design, and methods of the NPC trial are described in detail elsewhere (14). In brief, the NPC trial was a randomized, double-blind, placebo-controlled

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Context

Research suggests that selenium supplements may improve glucose metabolism.

Contribution

The investigators examined the incidence of type 2 diabetes among participants in a clinical trial designed to assess the effects of selenium supplementation on skin cancer. Participants randomly assigned to receive selenium were more likely to develop type 2 diabetes than were those assigned to placebo.

Cautions

Diabetes was a secondary outcome of the original trial. The diagnosis was self-reported, and most participants were older and white.

Implication

Long-term selenium supplementation appears to increase the risk for type 2 diabetes.

—The Editors

study of 1312 participants who were recruited in 1983 to 1991 from 7 dermatology clinics in areas of low selenium consumption of the eastern United States. Randomization was blocked by time and stratified by clinic. Persons were eligible if they had a confirmed history of nonmelanoma skin cancer in the year before randomization, had an estimated life expectancy of 5 years, and had no reported internal cancer in the previous 5 years. Participants with a history of clinically important liver or kidney disorders were excluded. Because the primary aim of the trial was to determine the effects of selenium supplementation on nonmelanoma skin cancer, we excluded nonwhite persons. This restriction served to control the effects of skin pigmentation on the risk for skin cancer recurrence. As a result, almost all participants in the NPC trial were non-Hispanic white persons; about 1.4% ($n = 18$) of persons who were randomly allocated were identified as Hispanic, and some persons were from other ethnic groups. Although recruitment was sex-neutral, about three quarters of the participants were male. Of the 1316 persons recruited, random assignment was successful for 1312. At the end of the blinded treatment period on 1 February 1996, no participant was lost to vital follow-up, generating a total of 9301 person-years of follow-up. Self-reported adherence indicated that 79.3% of participants (80.3% in the placebo group and 78.4% in the selenium group) adhered to the intervention (16). This was corroborated by the fact that plasma selenium levels remained constant throughout the trial in the placebo group but were substantially higher in the selenium group (**Figure 1**).

We analyzed only participants with a valid baseline selenium value obtained within 4 days from the date of randomization (1250 of 1312 participants), a decision that is consistent with previously published studies from the NPC trial (15–17). Baseline characteristics of the total NPC cohort of 1312 participants and the subsample of 1250 participants with valid baseline selenium levels did not statistically significantly differ (17), and our findings did not change substantially when analyses were expanded to include all 1312 participants (data not reported).

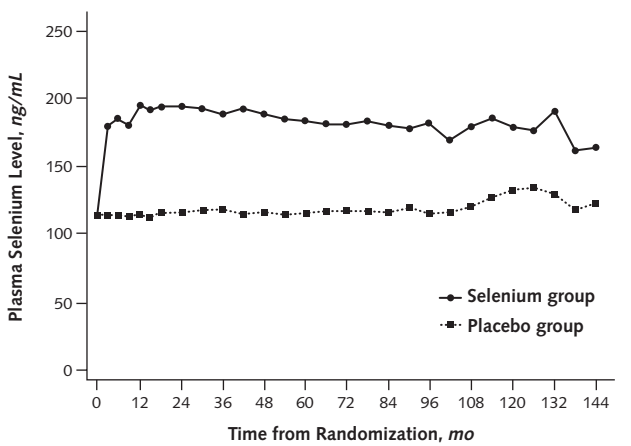
We focus on the 1202 participants who did not have type 2 diabetes at baseline (600 selenium recipients and 602 placebo recipients). Ascertainment of prevalent type 2 diabetes at baseline was based on a self-reported diagnosis of type 2 diabetes before randomization, with subsequent evaluation of medical records (48 cases [21 in the selenium group and 27 in the placebo group]). **Figure 2** shows the flow diagram of the NPC participants included in our analysis.

Clinical Examination and Laboratory Methods

The intervention agent was 200 μg of selenium daily, supplied in a 0.5-g, high-selenium baker's yeast tablet provided by Nutrition 21 (La Jolla, California) through 1995 and by Cypress Systems (Fresno, California) thereafter. The placebo group received a tablet containing yeast only. Selenium and placebo pills were coated with titanium oxide to ensure identical appearance and smell.

Each patient was assigned a unique sequential treatment number. Treatment group assignment was made centrally by using sealed identical pill bottles that were distributed at the clinic. The coordinating center held all treatment information in blinded form (14). The selenium content of each batch of pills was determined in the laboratories of Dr. Combs and of I.S. Palmer, MD (South Dakota State University, Brookings, South Dakota), by the diaminonapthalene fluorometric procedure after nitric–perchloric acid digestion (18). Plasma selenium level was determined in the laboratory of Dr. Combs by using an automated electrothermal atomic absorption spectropho-

Figure 1. **Mean plasma selenium levels.**



tometer (Perkin Elmer 3030, Perkin-Elmer, Norwalk, Connecticut) equipped with an electrodeless discharge lamp and automatic Zeeman-effect background correction. Quality control included multiple aliquots of human plasma as external control samples. A coefficient of variation less than 7% (for duplicate analyses) was the criterion for acceptance (19).

Participants visited their respective clinics biannually to provide blood samples and report new illnesses and medications. Patient medical records from both study and nonstudy visits were periodically reviewed to ensure completeness and accuracy. At the baseline interview, data were collected on sociodemographic, anthropometric, and behavioral characteristics, including education (0 to 18 years), body mass index (BMI), use of vitamin supplements, alcohol consumption (drinks consumed per day), smoking status (never, former, or current), and pack-years of smoking. For participants who became inactive, annual monitoring was attempted by using the National Death Index and ChoicePoint Services (formerly Equifax, Atlanta, Georgia) to determine vital status and identify diagnoses of new illnesses.

Ascertainment of Type 2 Diabetes and Follow-up

Participants who had a new diagnosis of type 2 diabetes during the blinded phase of the trial (15 September 1983 to 1 February 1996) were noted. The initial report of diabetes came from 3 sources: self-report during the clinical interview, reported use of drugs for diabetes, and reports in medical record documents. Medical record requests were then sent to the primary physicians for every patient with a report. This process of requesting and reviewing documentation was done in a blinded manner. About 92% of these reports, regardless of source, were corroborated with medical record documentation, as determined by registered nurse reviewers.

Person-years of follow-up were accrued from the date of randomization as the start date to the date of an incident case of type 2 diabetes, the date of death, or the end of the blinded period of the trial.

Statistical Analysis

For continuous and categorical variables, we used *t* tests and chi-square tests, respectively, to determine the statistical significance of any difference in the distribution of baseline variables between treatment groups. Cumulative incidence curves of type 2 diabetes by treatment group were constructed by comparing Nelson–Aalen cumulative hazard function estimates that were calculated at different time points of the trial and by using the 2-sided log-rank test (20). In unadjusted analyses, incidence data were statistically analyzed by calculating relative risks as the ratios of the incidence density for the treatment groups, with corresponding 95% CIs. *P* values were derived from log-rank tests. In adjusted analyses, hazard ratios and 95% CIs were calculated by using the Cox proportional hazard model, which allowed adjustment for age, BMI (continuous variable), sex, and smoking status at baseline as covariates. We decided a priori to adjust for these diabetes risk factors regardless of whether they differed between treatment groups. Tests of proportional hazards assumptions were based on Schoenfeld residuals (21). The tests showed that the proportional hazard assumption was not violated for any variable used in the model. Modification of association by median age (65 years), sex, smoking status, and BMI tertiles at randomization was tested by using the Mantel–Haenszel test for heterogeneity in the unadjusted models. The statistical significance of the interaction between each baseline characteristic and treatment group, adjusted for other important baseline variables, was tested in Cox proportional hazards models that included this interaction and the corresponding main effect terms. None of these interactions achieved a conventional level of statistical significance ($P < 0.05$). Similarly, a test of interaction between selenium treatment and vitamin supplements was not significant and was therefore not included in the multivariate analysis.

We also assessed the statistical association between the incidence of type 2 diabetes and baseline plasma selenium level. On the basis of the distribution among the 1202 participants who did not have type 2 diabetes at baseline, we divided baseline plasma selenium levels at the median

Figure 2. **Flow diagram of the Nutritional Prevention of Cancer Trial, 1983–1996.**

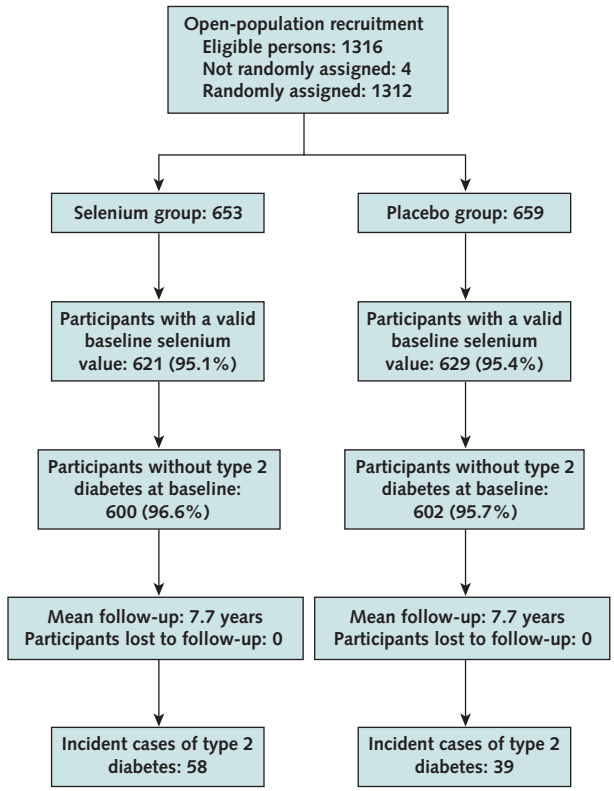


Table 1. **Baseline Characteristics***

Characteristic	Selenium Group	Placebo Group
Participants randomly assigned, *n*	600	602
Mean age (SD), *y*	63.4 (10.2)	63.0 (9.9)
Mean education (SD), *y*	12.9 (3.4)	12.9 (3.3)
Men, %	74.0	75.0
Mean body mass index (SD), kg/m^2	25.6 (3.9)	25.5 (4.1)
Mean follow-up (SD), *y*	7.7 (2.8)	7.7 (2.7)
Smoking status, %†		
Never	34.0	30.0
Former	39.0	40.0
Current	27.0	30.0
Mean pack-years of smoking (SD)	56.8 (40.3)	56.6 (39.0)
Mean alcohol use (SD), *drinks/d*‡	1.9 (3.1)	1.6 (2.9)
Plasma selenium level, *ng/mL*		
Mean (SD)	114.4 (22.6)	114.0 (21.5)
33rd percentile	105.6	104.8
50th percentile	113.6	113.2
66th percentile	122.4	121.2
Participants who use vitamin supplements, %	39.8	36.4

* No difference between treatment groups was statistically significant ($P \leq 0.05$).
† Calculated after excluding never-smokers.
‡ Calculated after excluding nondrinkers.

(≤113.4 ng/mL and >113.4 ng/mL) and at tertiles (≤105.2 ng/mL, 105.3 to 121.6 ng/mL, and >121.6 ng/mL). We assessed the association of selenium supplementation with the incidence of type 2 diabetes within these subgroups by using the same techniques as for analyses within subgroups of baseline age, BMI, sex, and smoking status. All statistical analyses were done by using STATA, version 9.0 (Stata, College Station, Texas).

Role of the Funding Source

This study was not supported by funding.

Results

Table 1 shows selected baseline characteristics of the 1202 participants at randomization. The treatment groups were well balanced for baseline characteristics, with no differences in the distribution of variables between groups.

During an average follow-up of 7.7 years (SD, 2.7), 97 new cases of type 2 diabetes were diagnosed overall, for an incidence of 10.5 cases per 1000 person-years. This rate is similar to that in other studies of largely white populations (22, 23). However, the cumulative incidence of type 2 diabetes was higher among those receiving selenium than among those receiving placebo throughout the trial (**Figure 3**). Of the 97 new cases of type 2 diabetes, 58 developed in the selenium group and 39 developed in the placebo group (incidence, 12.6 cases per 1000 person-years vs. 8.4 cases per 1000 person-years, respectively; hazard ratio, 1.55 [95% CI, 1.03 to 2.33]). The lack of benefit of selenium supplementation on the incidence of type 2 diabetes persisted when analyses were stratified by age, sex, smoking status, and BMI (**Table 2**).

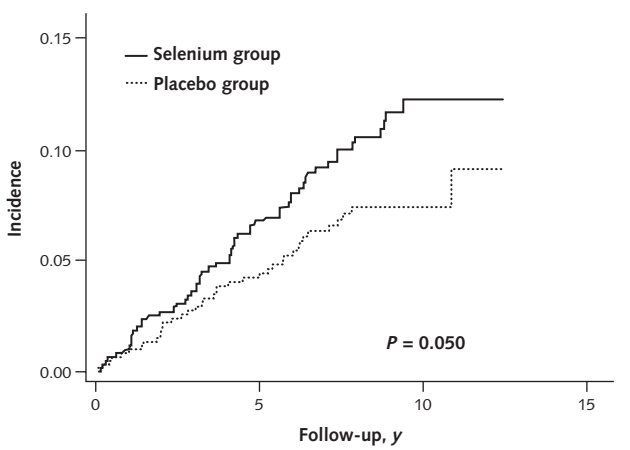
Despite the lack of statistically significant interactions between treatment group and baseline covariates, the risk for type 2 diabetes was consistently higher in the selenium group within all subgroups of baseline age, sex, smoking status, and BMI. However, in analyses stratified by BMI tertiles, the risk for type 2 diabetes did not differ between treatment groups within the top tertile of BMI.

Finally, because the published literature indicates that a relative deficiency of selenium may be associated with diabetes (12), we explored the effect of selenium supplementation on the incidence of type 2 diabetes within subgroups defined by the median and by tertiles of baseline plasma selenium level (**Table 3**). An exposure–response gradient ($P = 0.038$) was found across tertiles of baseline plasma selenium level, with a statistically significant increased risk for type 2 diabetes in the top tertile (hazard ratio, 2.70 [CI, 1.30 to 5.61]). Likewise, a statistically significant increased risk for type 2 diabetes was observed in individuals with plasma selenium levels greater than the baseline median value (hazard ratio, 2.50 [CI, 1.32 to 4.77]).

Discussion

We examined the effect of long-term supplementation with 200 μg of selenium daily on the incidence of type 2 diabetes during the blinded phase of the NPC trial (mean follow-up, 7.7 years) among 1202 participants who did not have type 2 diabetes at baseline. Selenium supplementation did not seem to confer benefit in terms of risk for type 2 diabetes in this sample of persons from low-selenium areas in the eastern United States. Instead, the cumulative incidence of type 2 diabetes was statistically significantly higher in the selenium group than in the placebo group. Examination of baseline covariates did not change the results, and risks for disease among participants receiving selenium were consistently higher across subgroups of baseline age, sex, smoking status, and BMI, except in participants within the top tertile of BMI. Moreover, the risk for type 2 diabetes associated with selenium supplementation

Figure 3. **Cumulative incidence of type 2 diabetes.**



The *P* value was derived from the log-rank test.

Table 2. **Incidence of Type 2 Diabetes**

Characteristic	Cases, *n*		Cumulative Incidence, *cases per 1000 person-years*		Relative Risk (95% CI)*	Log-Rank *P* Value	*P* Value for Heterogeneity†	Hazard Ratio (95% CI)‡	*P* Value‡	*P* Value for Interaction§
	Selenium Group	Placebo Group	Selenium Group	Placebo Group						
All participants	58	39	12.6	8.4	1.50 (0.98–2.30)	0.05		1.55 (1.03–2.33)	0.03	
Age										
≤65 y	25	18	9.8	6.7	1.47 (0.77–2.85)	0.21	0.81	1.53 (0.83–2.82)	0.17	0.88
>65 y	33	21	15.9	10.8	1.47 (0.83–2.67)	0.16		1.60 (0.92–2.76)	0.09	
Sex										
Female	9	8	6.8	6.3	1.10 (0.37–3.22)	0.87	0.46	1.38 (0.52–3.64)	0.51	0.54
Male	49	31	14.8	9.2	1.60 (1.00–2.61)	0.04		1.62 (1.04–2.55)	0.03	
Smoking status										
Never	15	12	9.1	8.2	1.11 (0.49–2.60)	0.74	0.65	1.16 (0.54–2.49)	0.70	0.53
Former	30	18	17.2	10.0	1.74 (0.94–3.30)	0.06		1.67 (0.93–3.00)	0.09	
Current	13	9	10.4	6.6	1.58 (0.63–4.19)	0.30		1.70 (0.71–4.00)	0.24	
Body mass index										
<23.71 kg/m^2	11	6	6.7	3.5	1.94 (0.66–6.38)	0.18	0.11	1.76 (0.64–4.80	0.27	0.15
23.72–26.76 kg/m^2	20	6	12.6	4.2	3.09 (1.21–9.16)	0.01		2.81 (1.12–7.04)	0.03	
>26.76 kg/m^2	27	27	19.6	19.1	1.02 (0.58–1.81)	0.90		1.09 (0.64–1.87)	0.74	

* Derived from incidence rate ratios.
† Mantel–Haenszel test.
‡ Derived from a Cox proportional hazards model adjusted for age, sex, body mass index, and smoking status.
§ For (treatment group × factor) cross-product term in a separate Cox proportional hazards model.

increased statistically significantly with greater baseline plasma selenium levels. Thus, these findings indicate no overall efficacy of selenium supplementation in the primary prevention of type 2 diabetes; conversely, they suggest that long-term supplementation with 200 μg of selenium daily may adversely affect glucose metabolism. The findings are potentially important because selenium supplements in doses of 30 to 200 μg are widely used by the public in the United States and other Western countries (24).

Whereas many observational studies, a few randomized clinical trials, and a meta-analysis have addressed the role of selenium as a cardiovascular protective factor (15, 25), few data are available on the effects of selenium on insulin resistance and risk for type 2 diabetes in humans. Experimental evidence from in vivo and in vitro studies suggests that selenium may mediate many insulin-like actions, thus enhancing insulin sensitivity (7–9). Potential adverse effects on glucose metabolism have been described in animal models of high-selenium diets (10). McClung and colleagues (26) reported the development of insulin resistance and obesity in mice with elevated expression of glutathione peroxidase 1, which is the most abundant selenoprotein in mammals. Li and associates (27) found that overexpression of catalase and metallothionein, 2 cytoplasmic antioxidants, accelerated spontaneous diabetes and altered insulin signaling in mice.

A few investigations have specifically addressed the effects of selenium on glucose metabolism and type 2 diabetes in humans. In a study examining the effects of 3 months of dietary selenium supplementation on biomark-

Table 3. **Incidence of Type 2 Diabetes, by Baseline Plasma Selenium Level**

Baseline Plasma Selenium Level	Cases, *n*		Cumulative Incidence, *cases per 1000 person-years*		Relative Risk (95% CI)*	Log-Rank *P* Value	*P* Value for Heterogeneity†	Hazard Ratio (95% CI)‡	*P* Value‡	*P* Value for Interaction§
	Selenium Group	Placebo Group	Selenium Group	Placebo Group						
Median										
≤113.4 ng/mL	26	25	11.1	10.7	1.03 (0.57–1.86)	0.89	0.06	1.04 (0.60–1.80)	0.89	0.028
>113.4 ng/mL	32	14	14.1	6.1	2.31 (1.20–4.69)	0.007		2.50 (1.32–4.77)	0.005	
Tertile										
≤105.2 ng/mL	18	18	11.6	11.3	1.03 (0.50–2.09)	0.92	0.21	1.13 (0.58–2.18)	0.72	0.038
105.3–121.6 ng/mL	14	10	8.8	6.5	1.35 (0.56–3.40)	0.46		1.36 (0.60–3.09)	0.63	
>121.6 ng/mL	26	11	17.5	7.3	2.40 (1.14–5.39)	0.01		2.70 (1.30–5.61)	0.008	

* Derived from incidence rate ratios.
† Mantel–Haenszel test.
‡ Derived from a Cox proportional hazards model adjusted for age, sex, body mass index, and smoking status.
§ For (treatment group × factor) cross-product term in a separate Cox proportional hazards model.

ers of vascular complications in 56 patients with type 2 diabetes, patients who received selenium had a statistically significant reduction in the activity of nuclear factor-κB (11). Findings from the Health Professionals Follow-up Study showed lower toenail levels of selenium among diabetic men (with or without cardiovascular disease) than among healthy control participants (12). Although the SU.VI.MAX trial showed no effect of combined supplementation with antioxidants, including selenium (100 μg/d), on fasting plasma glucose levels after 7.5 years of follow-up (13), analysis of the longitudinal association of baseline plasma antioxidants and fasting plasma glucose (at both baseline and follow-up) revealed a statistically significant association between baseline plasma selenium levels and fasting plasma glucose levels. Furthermore, Chen and coworkers (28) reported a strongly positive correlation between glutathione peroxidase activity and insulin resistance in nondiabetic women during normal pregnancy. Finally, a recent study of 8876 persons in the United States reported that many people had blood selenium levels that were higher than the lower limit of the upper tertile in the NPC trial and that high serum selenium levels (≥137.66 ng/mL) were associated with diabetes (29).

To our knowledge, our study is the largest completed randomized clinical trial to date that has examined the efficacy of selenium supplementation alone in the prevention of type 2 diabetes. The results indicate that long-term selenium supplementation at 200 μg/d may increase the risk for diabetes, thus raising concerns about the prolonged use of dietary supplements with selenium in terms of glucose metabolism and insulin resistance.

Evidence on potential mechanisms that explain these findings is limited. Selenium is a trace mineral with a narrow therapeutic window and large interindividual variability in metabolic sensitivity (30, 31). Much has been published on the adverse health effects of long-term exposure to selenium compounds in humans. In particular, the endocrine system may show early manifestations of toxicity induced by excess selenium. For example, Hawkes and Keim (32) reported the onset of subclinical hypothyroidism in healthy men given a high-selenium diet (about 300 μg/d) for 99 days, leading to body weight increases. Dietary selenium may adversely affect growth hormone metabolism by suppressing the production of insulin-like growth factor I (33), which has a documented influence on the control of glucose homeostasis (34). Data from animal models suggest that high-selenium diets may stimulate the release of glucagon, thus leading to hyperglycemia (10). Finally, the NPC trial was conducted in a region where the average dietary selenium intake is 90 μg/d; this value is low for the United States but is much greater than that required to optimize selenoenzyme activities (35). In particular, the upper value of the bottom tertile in our analysis (105.2 ng/mL) is greater than the level needed for optimal activity of glutathione peroxidase; thus, long-term supplementation with 200 μg of selenium daily may have led to overexpression of this enzyme, which in turn may have contributed to these unexpected results, as found in animal models (26, 27).

Despite our findings, some evidence suggests that selenium supplementation may have a role in cancer prevention (16, 17). Ongoing, large randomized clinical trials are addressing this question and will probably provide more convincing evidence (36).

Our study has limitations. First, the incidence of diabetes was not a primary end point of the NPC trial. Our findings must be interpreted cautiously because they result from exploratory analyses, albeit from the largest completed randomized clinical trial in which selenium alone was the intervention.

Second, diagnosis of type 2 diabetes was self-reported, which may have led to some misclassification (underdiagnosis) at baseline or during the trial. However, given the randomized design, blinding, and documentation of the diagnosis by using medical records in our study, differential misclassification according to treatment assignment is unlikely. The effect of nondifferential misclassification would probably be to underestimate the true relative risk and decrease the statistical power of our study (37). However, the incidence rates that we observed are similar to national figures in the United States (38).

Third, although the incidence estimates were adjusted for potential confounders, such as age, sex, smoking status, and BMI, detailed information on unmeasured risk factors at baseline, such as family history of diabetes, body fat distribution, and physical activity, are lacking. However, randomization should have minimized the likelihood of confounding by these factors, as shown by the lack of significant differences in the evaluated baseline characteristics between treatment groups.

Fourth, the NPC sample consisted of elderly individuals (mean age, 63.2 years) from low-selenium areas in the eastern United States who had a history of nonmelanoma skin cancer. The generalizability of our findings to other groups may therefore be limited.

Finally, we cannot rule out the role of chance in our findings. The exposure–response gradient across tertiles of baseline plasma selenium levels seems to indicate that the observed associations are unlikely to be due to chance. However, a few more cases of diabetes in the placebo group would attenuate the main effect of selenium treatment and produce null findings.

In contrast to the limitations, a strong point of our study is the high adherence to the intervention, as indicated by the constant differences in plasma selenium levels between treatment groups throughout the trial.

In summary, we found no overall efficacy of supplementation by selenium alone in the prevention of type 2 diabetes. In contrast, long-term dietary supplementation with selenium may increase risk for this disease.

From the State University of New York at Buffalo and Cancer Prevention and Population Sciences, Roswell Park Cancer Institute, Buffalo, New York; Clinical Sciences Research Institute, Warwick Medical School, Coventry, United Kingdom; and U.S. Department of Agriculture Human Nutrition Research Center, Grand Forks, North Dakota.

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Requests for Single Reprints: Saverio Stranges, MD, PhD, Clinical Sciences Research Institute, Warwick Medical School, University Hospital Coventry and Warwickshire, Clifford Bridge Road, Coventry CV2 2DX, United Kingdom; e-mail, s.stranges@warwick.ac.uk.

Current author addresses and author contributions are available at www.annals.org.

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Current Author Addresses: Drs. Stranges, Cappuccio, and Ceriello: Clinical Sciences Research Institute, Warwick Medical School, University Hospital Coventry and Warwickshire, Clifford Bridge Road, Coventry CV2 2DX, United Kingdom.

Drs. Marshall and Reid and Mr. Natarajan: Roswell Park Cancer Institute, Carlton House Building, Elm and Carlton Streets, Buffalo, NY 14263.

Drs. Donahue and Trevisan: Department of Social and Preventive Medicine, State University of New York at Buffalo, South Campus, 3435 Main Street, Farber Hall, Buffalo, NY 14214.

Dr. Combs: Human Nutrition Research Center, U.S. Department of Agriculture, 2420 Second Avenue North, Stop 9034, Grand Forks, ND 58202.

Author Contributions: Analysis and interpretation of the data: S. Stranges, R. Natarajan, R.P. Donahue, M. Trevisan, G.F. Combs, F.P. Cappuccio.

Drafting of the article: S. Stranges, R.P. Donahue, M. Trevisan.

Critical revision of the article for important intellectual content: S. Stranges, R.P. Donahue, M. Trevisan, G.F. Combs, F.P. Cappuccio.

Final approval of the article: S. Stranges, M. Trevisan, F.P. Cappuccio.

Statistical expertise: R. Natarajan, M. Trevisan.

Administrative, technical, or logistic support: G.F. Combs, F.P. Cappuccio.

Collection and assembly of data: G.F. Combs.